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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,481	DE GRAAF	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-35,37-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35, 37-46 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (e.g., see 3/4/05 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/6/04 has been entered. Claims 32-51 were pending. Applicants amended claims 32, 37 and 42. In addition, Applicants canceled claims 36 and 47. Therefore, claims 32-35, 37-46 and 48-51 are pending and examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

3. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to

the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

With respect to adequate disclosure Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention*. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure).

In this case, the number of claimed nucleic acid sequences is very large. Applicants claim recombinant vectors of any origin (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.) using any snRNA (U1, U2, U3 ... etc.) using any restriction enzyme. However, Applicants provide only ONE example in the specification drawn to a pSP-luc+ plasmid using 293T cells and a U1 snRNA with the BaeI enzyme (e.g., see specification, pages 21-23). Consequently, it is the Examiner's position that one example is not representative of the infinite number of vectors that are currently claimed because the claims encompass a wide variety of different species (e.g., different origin, mechanism, host cell type). When there is substantial variation within the genus, one

must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). In addition, the more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

The CAFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)] (the case is referred to herein as "*Lilly*"). Here, the instant claims define the components of the recombinant vector only by their functional properties (e.g., ability to splice). The CAFC held this sort of functional definition insufficient to adequately describe the claimed product.

Response

4. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... the number of claimed nucleic acid sequences as amended is not very large because the restriction enzyme belongs to a unique family of restriction endonucleases that excise a fragment containing the recognition site" (e.g., see 12/6/04 Response, pages 5-6, especially page 6, middle paragraph).

[2] Applicants argue, "a wide variety of appropriate vectors for use in the invention as claimed were well known in the art" and quote the Guidelines for the Examination of Patent Applications Under the Written Description Requirement stating, "[i]nformation which is well known in the art need not be descried in detail in the specification" (e.g., see 12/6/04 Response, pages 6-7).

This is not found persuasive for the following reasons:

[1] Applicants' arguments are not commensurate in scope with the claims. Applicants state that the scope of the claims is now limited to a smaller "unique family" of restriction endonucleases that excise a fragment containing the "recognition" site of the restriction enzyme. However, this assertion appears to be in error. The claims disclose only a "restriction" site, not a "recognition" site as purported by Applicants. In addition, it is not clear what the metes and bounds of the "restriction" site are (e.g., see 35 U.S.C. 112, second paragraph).

Thus, Applicants' single example is not representative of the broad scope that is currently being claimed. Furthermore, it is again noted that there is a greater need for representative examples in an unpredictable art. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). For example, the Board has held that "the unpredictability of an art area alone may be

enough to create a reasonable doubt as to the accuracy of statements in the specification." Ex parte Singh, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990). Thus, when claims encompass a broad genus (as is the case here) with widely varying structures that would not be expected to function in a similar manner due to their diverse nature (e.g., the vectors are of ***any*** origin (e.g., viral, plasmid, etc.) that can infect host cells of ***any*** type (e.g., human, bacterial, yeast, etc.) via ***any*** mechanism (e.g., replicate, integrate, etc.) using ***any*** restriction enzyme) then a greater showing in the specification must be set forth. This has not been done. Consequently, the Examiner contends that Applicants' claimed scope represents only an invitation to experiment.

[2] When there is little to no disclosure in the instant specification of the starting material or conditions under which claimed process can be carried out, this failure cannot be rectified by asserting that all disclosure related to the process is within skill of art. *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 (3/13/1997). Furthermore, the Court has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990). Thus, in applications directed to inventions in arts where the results are unpredictable, ***the disclosure of a single species usually does not provide an adequate basis to support generic claims***. *In re Soll*, 97 F.2d 623, 624, 38USPQ 189, 191 (CCPA 1938). Here, Applicants provide only one example in a field with enormous breadth and variability.

Accordingly, the written description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

5. Claims 32-34, 41, 42, 44-46, 48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**).

For ***claims 32 and 42***, Noonberg et al. (see entire document) disclose ribozyme oligonucleotide constructs (e.g., see Noonberg et al., abstract), which anticipate the claimed invention. For example, Noonberg et al. disclose a recombinant vector comprising an isolated nucleotide sequence encoding a snRNA (e.g., U6), wherein said nucleotide sequence [i.e., vector] has been modified to contain one or more restriction sites [i.e., SmaI], such that digestion with a single restriction enzyme excises a restriction fragment [i.e., U6] which includes a restriction site for said restriction enzyme [i.e., the blunt ends of SmaI cleavage site] and forms insertion sites in said nucleotide sequence [e.g., SmaI insertion site is useful for cloning] (e.g., see Example 3, "The human U6 gene [snRNA] cloned within the [single] SmaI site of pGem1 [recombinant vector]"' see also 35 U.S.C. 112, second paragraph below showing that it is not possible to determine the metes and bounds of "restriction site").

In addition, Noonberg et al. disclose "two insertion sites" (i.e., the 3' and 5' blunt ends of the SmaI linearized pGem1), which are formed by the digestion of a single SmaI endonuclease. In this scenario, the library of U6 represent the "cassette" (e.g., see figures 4B and 9 wherein a U6 snRNA vector is shown that has XhoI and NsiI restriction sites for inserting synthetic sequences; see also page 25, paragraph 2; see also page 36, paragraph 2; see also page 41, last paragraph;

see especially page 50,; see also page 56, paragraph 2; see also claim 24; see also page 9, lines 9-10; see page 35, paragraph 1, "The oligonucleotides can be designed for binding to different regions of different DNA or RNA targets, to different regions of the same DNA or RNA target, or to the same region of the same DNA or RNA target. Decisions as to vector design would be based upon whether the experimenter wanted to hit multiple targets broadly or a single target intensely"; see also figure 2(a) wherein the insertion of multiple oligos [i.e., a cassette] are shown; see also page 6, line 10; see also page 8, line 1; see also page 10, line 18; see also page 15, first full paragraph; see also page 38, line 31; see also page 39, lines 8-13; see also page 40, last paragraph; see also page 43, last paragraph; see also page 49, Example 2; see also page 2, Antisense section).

For ***claims 33-34 and 44-45***, Noonberg et al. disclose, for example, U6 snRNAs (e.g., see figure 4; see also page 50, Example 3; see also page 38, line 10; see also figures 19-21; see also pages 22-23; see also page 87, paragraph 2-3; see also page 93, last paragraph).

For ***claim 48***, Noonberg et al. disclose any restriction site including XhoI, NsiI wherein the restriction sites are excised to produce a double stranded insert (e.g., see page 33, paragraph 2, "Of course the XhoI and NsiI restriction sites can be replaced with ***any*** first and second unique restriction enzyme sites to facilitate insertion of the specific nucleotide sequence").

For ***claim 41 and 51***, Noonberg et al. disclose overhanging ends that are complementary (e.g., see page 51, line 7).

For ***claim 46***, Noonberg et al. disclose 30 bp insert (e.g., see page 50, Example 3 wherein insert is U6 gene from +25 to +55, which is 30 bp long).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Noonberg et al. disclose a vector comprising two restriction sites of two different restriction enzymes (e.g., XhoI and NsiI), and digesting the vector with two different restriction enzymes" (e.g., see 12/6/04 Response, page 7, especially last paragraph).

[2] Applicants argue, "Further, the restriction fragment from the digestion would not contain the recognition sites for the restriction enzymes because the restriction enzymes (e.g., XhoI and NsiI) cut within their sites (e.g., see 12/6/04 Response, page 7, last paragraph).

[3] Applicants argue, "Noonberg et al. disclose insertion of an insetion cassette into their vector, the resultant construct would be different from the one as claimed in claim 42 because, as argued above, the Noonberg vector differs from the vector in claim 32 at least in the restriction site, restriction enzyme, and restriction fragment" (e.g., see 12/6/04 Response, page 8, paragraphs 1-3)

This is not found persuasive for the following reasons:

[1] The Examiner contends Noonberg et al. disclose a "single" restriction site (e.g., see newly amended rejection wherein SmaI is disclosed).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "recognition" site) are not recited in the rejected claim(s) (see also 35 U.S.C. 112, second paragraph below showing that it is not clear what constitutes a "restriction" site). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[3] To the Extent that Applicants are reiterating their arguments for claim 32, the Examiner contends that those issues were adequately addressed in sections **[1]**-**[2]** above.

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

7. Claims 32-35, 41-46, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**) and the admission of prior art in the Specification and Cohen et al. (Cohen, J. B.; Snow, J. E.; Spencer, S. D.; Levinson, A. D. "Suppression of mammalian 5' splice-site defects by U1 small nuclear RNAs from a distance" PNAS 1994, 91, 10470-10474) (see IDS 3, reference AT) and Tuschl et al. (Tuschl, T.; Sharp, P. A.; Bartel, D. P. "Selection in vitro of novel ribozymes from a partially randomized U2 and U6 snRNA library" EMBO **1998**, 17, 9, 2637-2650).

For ***claims 32-34, 41, 42, 44-46, 48 and 51***, Noonberg et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious 32-34, 41, 42, 44-46, 48 and 51.

The prior art teachings of Noonberg et al. differ from the claimed invention as follows:

For ***claims 35 and 43***, Noonberg et al. is deficient in that it does not specifically teach the use of U1 snRNA recombinant vector or U1 snRNA recombinant vector with insertion cassette wherein the sequence has been modified within the first 11 nucleotides of the coding region.

However, the admission in the specification and the Cohen et al. and Tuschl et al. references teach the following limitations that are deficient in Noonberg et al.:

For ***claims 35 and 43***, Tuschl et al. (see entire document) discloses a recombinant vector encoding U2 and U6 snRNA with a 40 nucleotide insertion cassette contained between two insertions sites (see Tuschl et al., figures 1-2, see also Materials and Methods, Pool Construction, selection and amplification). Furthermore, the admission in the specification combined with the reference that the specification refers to (i.e., the Noonberg et al. reference) teach that a person of skill in the art would recognize the value of using any U snRNA including U1 snRNA extending the teaching of Tuschl et al. from U2/U6 to U1 snRNA (e.g., see specification, Background of the Invention, page 1, last paragraph, "There has long been interest in utilizing the various splicing functions of individual U

snRNA to inhibit or modify transcription, and, thereby, to suppress undesired expression products (Cohen, J. B., et al., 1994, PNAS 91:10470-10474) [which specifically cites the use of U1 snRNA, see entire document, especially abstract and Materials and Methods section]). Such suppression has enormous therapeutic potential"). Furthermore, Cohen et al. teach a modification within the first 11 nucleotides (e.g., see Figure 3 A, U1-αA5 which has a mutation in the "fifth" position which is within the first eleven nucleotides).

It would have been obvious to one skilled in the art at the time the invention was make a recombinant vector encoding snRNA with an insertion cassette as taught by Noonberg et al. with the U1 snRNA cassette vector as taught by the admission in the specification and the Cohen et al. and Tuschl et al. references because the admission in the specification teach that any U snRNA would be a candidate for recombinant technology and specifically points to U1 snRNA by citing the Cohen et al. reference (see specification, page 1, last paragraph; see also Cohen et al. reference, entire document). Furthermore, one of ordinary skill in the art would have been motivated to use the U1 snRNA as taught by the admission in the specification and Cohen et al. because according to the specification modification of such a snRNA would have "enormous therapeutic potential" and specifically recites a reference (i.e., the Cohen et al. reference) that addresses the use of U1 snRNA. In addition, Noonberg et al. teach that their invention is "an improved method" for the delivery of ribozymes (e.g., see Noonberg et al., page 1, line 24; see also page 14, line 27; see especially page 24, last paragraph), which would encompass the ribozymes disclosed by Cohen et

al. and Tuschl et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all the references teach that recombinant U snRNAs can be made into a vector and mutated. In addition, Noonberg et al. states that "***any*** oligonucleotide that is desired to be transcribed within the cell [can be used] ... including ... a ribozyme" (e.g., see paragraph bridging pages 29-30), which specifically points toward the ribozyme papers of Cohen et al. and Tuschl et al. Furthermore, Noonberg et al. states that the advantages of using their invention with ribozymes like those disclosed by Cohen et al. and Tuschl et al. are that "RNA polymerase III transcribes at a nearly constant rate and high frequency in almost all mammalian cell types ... [and] are also highly efficient allowing for clean transcription" (e.g., see Cohen et al., page 36, first full paragraph).

8. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**) and the admission of prior art in the Specification and Cohen et al. (Cohen, J. B.; Snow, J. E.; Spencer, S. D.; Levinson, A. D. "Suppression of mammalian 5' splice-site defects by U1 small nuclear RNAs from a distance" PNAS 1994, 91, 10470-10474) (see IDS 3, reference AT) and Tuschl et al. (Tuschl, T.; Sharp, P. A.; Bartel, D. P. "Selection in vitro of novel ribozymes from a partially randomized U2 and U6 snRNA library" *EMBO* **1998**, *17(9)*, 2637-2650) (of record) and Sears et al. (Sears, L. E.; Zhou, b.; Aliotta, J. M.; Morgan, R. D.; Kong, H. "BaeI, another unusual BcgI-like restriction endonuclease" *Nucleic Acids Research* **1996**, 24(18), 3590-3592).

For ***claims 32-35, 41-46, 48 and 51***, the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 32-35, 41-46, 48 and 51.

The prior art teaching of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification differ from the claimed invention as follows:

For ***claims 37-40 and 49-50***, the prior art teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification differ from the claimed invention by not specifically reciting the use of a BaeI or the complements of DNA sequences of SEQ ID NO: 2 and SEQ ID NO: 3. The prior art teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification only state that "any first and second unique restriction enzyme sites to facilitate insertion of the specific nucleotide sequence" can be used and provide XhoI and NsiI as examples, but do not explicitly refer to BaeI (e.g., see Noonberg et al., page 33, paragraph 1).

However, Sears et al. teach the following limitations that are deficient in the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification:

For ***claims 37-40 and 49-50***, Sears et al. (see entire document) teach the use of BaeI on double stranded DNA (e.g., see Sears et al., figure 2-4). In

addition, the Examiner argues that the insertion sites produced by BaeI would "inherently" produce SEQ ID NO:2 and SEQ ID NO:3 because Applicants explicitly state, "its [i.e., BaeI] cleavage sites are 5'-GCAGG-3' (SEQ ID NO: 2) and 5'-TGAGA-3' (SEQ ID NO:3)" (see specification, page 18, first full paragraph). Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01.

It would have been obvious to one skilled in the art at the time the invention was made to make the recombinant snRNA vectors as taught by the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification with the BaeI restriction enzyme as taught by Sears et al. because Noonberg et al. explicitly states that any restriction enzyme can be used (e.g., see Noonberg et al., page 33, paragraph 1), which would encompass BaeI. Furthermore, one of ordinary skill in the art would have been motivated to use BaeI and would have reasonably expected to be successful because Sears et al. teach that BaeI can be used advantageously with double-stranded DNA (e.g., see Sears et al., abstract), which would include the dsDNA vectors disclosed by

the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification.

Response

9. Applicant's arguments directed to the Tuschl et al. 35 U.S.C. § 103(a) rejection (e.g., see 10/29/2003 Response, pages 9-10) were fully considered (and are incorporated in their entirety herein by reference) as they apply to the new 35 U.S.C. §103(a) rejection cited above but were not deemed persuasive.

[1] Applicant argue, ""reliance on the specification as filed for providing motivation to combine the two references impermissible" and cite MPEP § 706.02 (j) in support of this position, which states, "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not be based on applicants' disclosure" (e.g., see 12/6/04 Response, page 9, paragraph 2).

[2] Applicants argue, "Applicants submit that in view of the arguments presented above, Noonberg et a. do not teach all the elements of the claimed invention" (e.g., see 12/6/04 Response, pages 8-9, especially page 9, third full paragraph).

[3] Applicants argue, "Cohen et al. do not teach or suggest the restriction enzyme, restriction sites, or the restriction fragment as recited in claims 32 and 42" (e.g., see 12/6/04 Response, page 9, fourth full paragraph).

[4] Applicants argue, "Tuschl et al. do not teach the restriction enzyme, restriction sites, or the restriction fragment as recited in amended claims 32 and 42" (e.g., see 12/6/04 Response, page 9, fifth full paragraph).

[5] Applicants argue, "Even if combined, Noonberg et al., Cohen et al., and Tuschl et al. do not teach all the elements of the invention of claim 32 or 42" (e.g., see 12/6/04 Response, page 9, last paragraph).

[6] Applicants argue, "the cited references, taken singly or in combination, do not provide an incentive or motivation to make the combination" (e.g., see 12/6/04 Response, page 10, paragraph 1).

[7] Applicants argue, "Sears et al. do not teach or suggest use of the BaeI enzyme or similar enzymes in making the vector encoding an snRNA as recited in claims 32 or 42" (e.g., see 12/6/04 Response, page 10, paragraphs 2-4, especially paragraph 4).

[8] Applicants argue that there is no motivation to combine the references with Sears et al. (e.g., see 10/6/04 Response, page 10, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees (e.g., MPEP § 2129, "When applicant states that something is prior art, it is taken as being available as prior art against the claims. ***Admitted prior art can be used in obviousness rejections***." *In re Nomiya*, 509 F.2d 566, 184 USPQ 607, 611 (CCPA 1975) (Figures in the application labeled "prior art" held to be an admission that what was pictured was prior art relative to applicant's invention)). In addition, the Examiner notes that motivation can be provided either in the references themselves OR in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. MPEP § 2143. Here, Applicants have clearly admitted that "[t]here has long been interest [i.e., it was known in the prior art or, in the alternative, was knowledge generally available to one of ordinary skill in the art] in utilizing U snRNA [including U1 as exemplified by the "prior art"

reference of Cohen et al.] for their "enormous therapeutic potential" (e.g., see specification, Background of the Invention, page 1, last paragraph, "There has long been interest in utilizing the various splicing functions of individual U snRNA to inhibit or modify transcription, and, thereby, to suppress undesired expression products (Cohen, J. B., et al., 1994, PNAS 91:10470-10474) [which specifically cites the use of U1 snRNA, see entire document, especially abstract and Materials and Methods section]). Such suppression has enormous therapeutic potential"). Thus, the Examiner has not "impermissible" relied on Applicants' specification.

[2] The Examiner contends that to the extent that Applicants are reiterating their arguments to the "above" rejection, those issues were adequately addressed in that section (which is incorporated in its entirety herein by reference).

[3-4] In response to applicant's arguments against the Cohen et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[5] The Examiner contends that Noonberg et al. alone teaches all the elements of the invention as set forth in claims 32 and 42 (e.g., see newly amended 35 U.S.C. § 102 rejection above) and, as a result, the combined references must necessarily teach all the claimed limitations as well.

[6] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Here, Furthermore, one of ordinary skill in the art would have been motivated to use the U1 snRNA as taught by the admission in the specification and Cohen et al. because according to the specification modification of such a snRNA would have "enormous therapeutic potential" and specifically recites a reference (i.e., the Cohen et al. reference) that addresses the use of U1 snRNA. In addition, Noonberg et al. teach that their invention is "an improved method" for the delivery of ribozymes (e.g., see Noonberg et al., page 1, line 24; see also page 14, line 27; see especially page 24, last paragraph), which would encompass the ribozymes disclosed by Cohen et al. and Tuschl et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all the references teach that recombinant U snRNAs can be made into a vector and mutated. In addition, Noonberg et al. states that "***any*** oligonucleotide that is desired to be transcribed within the cell [can be used] ... including ... a ribozyme" (e.g., see paragraph bridging pages 29-30), which specifically points toward the ribozyme papers of Cohen et al. and Tuschl et al. Furthermore, Noonberg et al. states that the advantages of using their invention with ribozymes like those disclosed by Cohen et al. and Tuschl et al. are that "RNA polymerase III transcribes at a nearly constant rate and high frequency in almost all mammalian cell types ... [and] are also highly efficient allowing for clean transcription" (e.g., see Cohen et al., page 36, first full paragraph; see also section [1] above).

[7] In response to applicant's arguments against the Sears et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[8] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Here, one of ordinary skill in the art would have been motivated to use BaeI and would have reasonably expected to be successful because Sears et al. teach that BaeI can be used advantageously with double-stranded DNA (e.g., see Sears et al., abstract), which would include the dsDNA vectors disclosed by the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification

Accordingly, the 35 U.S.C. § 103 rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. To the extent that the deletion of the word "single" in claim 32 permits the encoding of more than one snRNA in the vectors (see also claim 42 which is likewise unlimited in the number of snRNAs), the increased breadth of possible modification constitutes new matter. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02. Therefore, claims 32, 42 and all claims represent new matter.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 32-35, 37-46 and 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 32, 37, and 42**, the term "restriction site" is vague and indefinite. For example, it is not clear whether the "restriction site" refers to the

"recognition site" or the "cleavage site" or some other sequence associated with the restriction enzyme such as a "partial recognition site" or a "partial cleavage site." For example, the FokI restriction enzyme cleaves at 9/13 bases away (i.e., the "cleavage site") from the GGATG "recognition" site regardless of the sequence at the cleavage site, which is represented by the "↓" (e.g., 5'-GGATGNNNNNNNNN↓N-3'). Does the "restriction site" constitute the "GGATG" portion or the "N↓N" portion or some nucleotides in between (e.g., "ATGN")? If the "restriction site" constituted the N↓N portion does this mean the "restriction site" can be any nucleotides? Consequently, the metes and bound cannot be determined. Therefore, claims 32, 37, 42 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 21, 2005

BENNETT CELSA
PRIMARY EXAMINER